Pyle, J.L., Kavalali, E.T., Piedras-Renteria, E.S., and Tsien, R.W. (2000). Neuron *28*, 221–231.

Sankaranarayanan, S., and Ryan, T.A. (2000). Nat. Cell Biol. *2*, 197–204.

Schneggenburger, R., and Neher, E. (2000). Nature *406*, 889–893.

Stevens, C.F., and Tsujimoto, T. (1995). Proc. Natl. Acad. Sci. USA *92*, 846–849.

Stevens, C.F., and Wang, Y. (1995). Neuron *14*, 795–802.

Stevens, C.F., and Williams, J.H. (2000). Proc. Natl. Acad. Sci. USA *97*, 12828–12833.

Sun, J.-Y., and Wu, L.-G. (2001). Neuron *30*, this issue, 171–182.

von Gersdorff, H., Vardi, E., Matthews, G., and Sterling, P. (1996). Neuron *16*, 1221–1227.

Vincent, P., and Marty, A. (1996). J. Physiol. *494*, 183–199.

Wang, L.-G., and Kaczmarek, L.K. (1998). Nature *394*, 384–388.

Wu, L.-G., and Betz, W.J. (1996). Neuron *17*, 769–779.

Wu, L.-G., and Borst, J.G. (1999). Neuron *23*, 821–832.

Nematodes Are Smarter than You Think

Weighing in at about 5 μg, with 302 neurons and 5000 synapses, *C. elegans* is unlikely to prove theorems, write poetry, or challenge Mike Tyson. Still, remarkable behavioral complexity is packed into this tiny worm. Worms live in a sensory world very different from our own, one dominated by touch, taste, and smell, one in which bacteria are the size of cherries, and Brownian motion and surface tension take the place of wind and gravity. It is difficult for us to intuit what their world is like, but one measure of what the worm cares about is the behavioral and genetic complexity devoted to various sensory modes. By this measure, thermotaxis must matter a lot to the worm. This behavior was first described in 1975 by Hedgecock and Russell, who noted, among other things, two remarkable features. First, worms are capable of moving along curving isothermal lines in their medium with precision, deviating as little as 0.1°C from their preferred temperature. Second, thermal preference is plastic, being conditioned by the presence or absence of food.

The plasticity in *C. elegans* thermotaxis is apt. When a worm experiences prosperity (abundant food) at a given temperature, it acquires a preference for this temperature over others. When the temperature is held steady and food is removed, this preference degrades with time and is replaced by a temperature-independent searching mode of locomotion. When food remains abundant and temperature is changed, the result is a gradual shift in thermal preference toward the new growth temperature. The assay for these changes is simple (Hedgecock and Russell, 1975). A conditioned worm is placed on an agar surface (without food) in which a radial thermal gradient has been formed. As the worm moves, it leaves behind a detectable indentation in the agar, providing a record of its locomotory behavior over time. A happily conditioned worm will spend most of its time making precise circles along its preferred isotherm. In the absence of other cues, the worm may anticipate that food is likely to be found at this temperature or it may simply be physiologically optimized at this temperature. In contrast, a worm conditioned by the absence of food will move in the same assay without regard for temperature as long as it remains within a tolerable range (Wittenburg and Baumeister, 1999). The main features of the neural circuit controlling thermotaxis are known. A single class of thermosensory neuron (AFD) makes synaptic output to a single class of interneuron (AIY). AIY in turn makes synapses mostly to three other classes of interneurons: AIZ, RIA, and RIB. AIZ makes synapses back to AIY and to various other interneurons. Based on synaptic connections, laser ablation studies, and genetic perturbations, AIY and AIZ are particularly important for thermotaxis, whereas RIA and RIB seem to be integrative interneurons that respond to many sensory cues (Mori and Ohshima, 1995; White et al., 1986, Hobert et al., 1997). AIY and AIZ play antagonistic roles in thermotaxis: AIY activity favors migration to high temperatures and AIZ activity favors low temperatures (Mori and Ohshima, 1995).

The paper by Gomez et al. (2001) in this issue of *Neuron* reports a role for a *C. elegans* neuronal Ca^{2+} sensor protein (NCS-1) in thermotaxis accuracy and plasticity. NCS-1 belongs to a large family of EF hand containing calcium binding proteins and is highly conserved across species, including yeast, *Drosophila*, *C. elegans*, rodents, and humans. They report that NCS-1 is expressed in 13 classes of neurons and one muscle cell. The neurons are mostly sensory, including the thermosensory neuron AFD, but they also include the interneuron AIY. The authors generate a null deletion allele of NCS-1 using reverse genetic methods (Plasterk, 1995). *ncs-1(null)* mutants develop normally and perform normally in chemotactic odorant responses, suggesting that their fine locomotory and taxis systems are unperturbed. However, their performance in isothermal tracking is substantially degraded, resembling that seen when the thermosensory neuron AFD is removed. Transgenic experiments with altered *ncs-1* genes show that its function in thermotaxis depends on its Ca^{2+} binding sites and on expression specifically in the interneuron AIY.

Up to this point, these results are interesting but, one might argue, not particularly exceptional: NCS-1 functions in AIY in its familiar Ca^{2+} binding role to mediate thermosensory response. However, perhaps inspired by similar approaches to the study of *Drosophila* learning and memory (Yin et al., 1995), the authors go on to make a very striking set of observations. Transgenic overexpression of normal NCS-1 protein from its own promoter enhances peak isothermal tracking accuracy, speeds the acquisition of a new thermal preference after temperature shift paired with food, and delays the extinction of thermal preference when food is removed. This is the kind of result every scientist dreams of: simple and compelling. It is hard to escape the conclusion that NCS-1 is a critical component of a process that mediates thermotaxis plasticity and memory. Are worms with more NCS-1 smarter? I doubt this is the right way to think about it. We can presume that the quality of isothermal tracking and the rate of change in thermal preference are adaptive traits. As with sensory attentiveness and long-term memory in humans, it is presumably important for worms to place a selectable weight on particular

sensory information and to modify existing associations with appropriate deliberation.

Naturally, it is tempting to speculate about the mechanistic role of NCS-1 in plasticity. However, the NCS family of proteins is sizeable, diverse, and largely unexplored. *C. elegans* appears to have five NCS-related genes and humans have perhaps a dozen (Burgoyne and Weiss, 2001), with different members implicated in processes as diverse as guanylyl-cyclase regulation (Palczewski et al., 1994), K^+ channel modulation (An et al., 2000), and protein kinase inhibition (Chen et al., 1995). A role in control of synaptic strength (e.g., Pongs et al., 1993), though mechanistically not yet understood, is the most promising in explaining the current results. This NCS-1 function is likely to be in the interneuron AIY, but whether it functions pre- or postsynaptically, at what synapse, and by what biochemical mechanism are all unknown. The pump has been primed, but much remains to be investigated.

James H. Thomas
Department of Genetics
University of Washington
Seattle, Washington 98195

Selected Reading

An, W.F., Bowlby, M.R., Betty, M., Cao, J., Ling, H.P., Mendoza, G., Hinson, J.W., Mattsson, K.I., Strassle, B.W., Trimmer, J.S., and Rhodes, K.J. (2000). Nature *403*, 553–556.

Burgoyne, R.D., and Weiss, J.L. (2001). Biochem. J. *353*, 1–12.

Chen, C.K., Inglese, J., Lefkowitz, R.J., and Hurley, J.B. (1995). J. Biol. Chem. *270*, 18060–18066.

Gomez, M., De Castro, E., Guarin, E., Sasakura, H., Kuhara, A., Mori, I., Bartfai, T., Bargmann, C.I., and Nef, P. (2001). Neuron *30*, this issue, 241–248.

Hedgecock, E.M., and Russell, R.L. (1975). PNAS *72*, 4061–4065.

Hobert, O., Mori, I., Yamashita, Y., Honda, H., Ohshima, Y., Liu, Y., and Ruvkun, G. (1997). Neuron *19*, 345–357.

Mori, I., and Ohshima, Y. (1995). Nature *376*, 344–348.

Palczewski, K., Subbaraya, I., Gorczyca, W.A., Helekar, B.S., Ruiz, C.C., Ohguro, H., Huang, J., Zhao, X., Crabb, J.W., Johnson, R.S., et al. (1994). Neuron *13*, 395–404.

Plasterk, R. (1995). Methods Cell Biol. *48*, 59–80.

Pongs, O., Lindemeier, J., Zhu, X.R., Theil, T., Engelkamp, D., Krah-Jentgens, I., Lambrecht, H.G., Koch, K.W., Schwemer, J., et al. (1993). Neuron *11*, 15–28.

White, J., Southgate, E., Thomson, J.N., and Brenner, S. (1986). Phil. Trans. R. Soc. Lond. B *314*, 1–340.

Wittenburg, N., and Baumeister, R. (1999). PNAS *96*, 10477–10482.

Yin, J.C., Del Vecchio, M., Zhou, H., and Tully, T. (1995). Cell *81*, 107–115.

Sleeper's Wake

Sleep has to be one of the Last Great Mysteries of animal physiology. For all we know about the phenomenon of sleep, we have, until recently, achieved little more than speculation as to what it does for the body. And yet sleep is as critical as any organ to health and well-being. Even short-term sleep deprivation has devastating effects throughout the body, on mental performance, immune function, endocrine function, and more. Long-term deprivation, whether induced experimentally in animals or induced by disease in humans, invariably leads to death. So our relative ignorance regarding the function of sleep, especially after years of studying its rhythms, its electrical signatures in the brain, its various stages, and its biochemistry, is all the more striking.

One of the proposed functions of sleep for which there is a considerable amount of evidence is memory consolidation. According to this view, sleep (and in particular REM sleep) is a period of little sensory input during which the brain rehearses or replays events or newly learned procedural tasks. The replay would then be required for these memories to be solidified in the brain. This idea is supported by a number of studies in both humans and animals showing that disrupting REM sleep reduces subsequent performance on simple memory tasks (Karni et al., 1994; Stickgold et al., 2000). Evidence of the replay itself comes from an elegant paper by Louie and Wilson (2001) recently published in Neuron and widely reported in the popular press. These authors recorded from several place neurons in the hippocampus as an animal ran a stereotyped path in a circular maze to receive a food reward. Given the repetitive path the animal took, the place neurons also fired in a stereotyped sequence as the animal repeatedly entered the place fields for each cell in turn. Following the maze running, the animals were allowed to sleep, and remarkably, the place neurons fired in sequences highly correlated to those recorded during the maze running. A similar effect has been observed in zebra finches in the period during which they learn their song. During sleep, the patterns of neuronal activity in a song-related nucleus (RA) are well correlated to the patterns present during song vocalization (Dave and Margoliash, 2000). While one must be cautious about interpreting these data as evidence for dreaming in animals or as evidence of memory consolidation, they are nevertheless suggestive in light of the consolidation hypothesis.

At the same time, however, the memory consolidation idea is not uncontroversial. In a recent review, Vertes and Eastman (2000) point out major difficulties with the supporting evidence. First, antidepressant drugs and some brainstem lesions suppress or even eliminate REM sleep, and yet cognitive performance in affected patients show little impairment. Second, only about half the animal studies looking for memory deficits after sleep deprivation have shown effects. Third, in many of these studies, sleep deprivation may have been confounded with stress. The sleep deprivation technique often used (placing the animal on a small platform above a pool of water) is itself stressful. The impairment of performance immediately following the deprivation period thus may be related to stress rather than sleep loss, and, indeed, some studies have shown that performance recovers some hours after the deprivation period. None of these findings are consistent with REM sleep being required for memory consolidation or retention.

Against the background of the controversy surrounding the role of sleep in memory, then, the paper by Frank et al. (2001) reported in this issue of *Neuron* is all the more interesting. These authors have not examined memory per se, but they examined a classical model of neuronal plasticity and found dramatic effects of short-